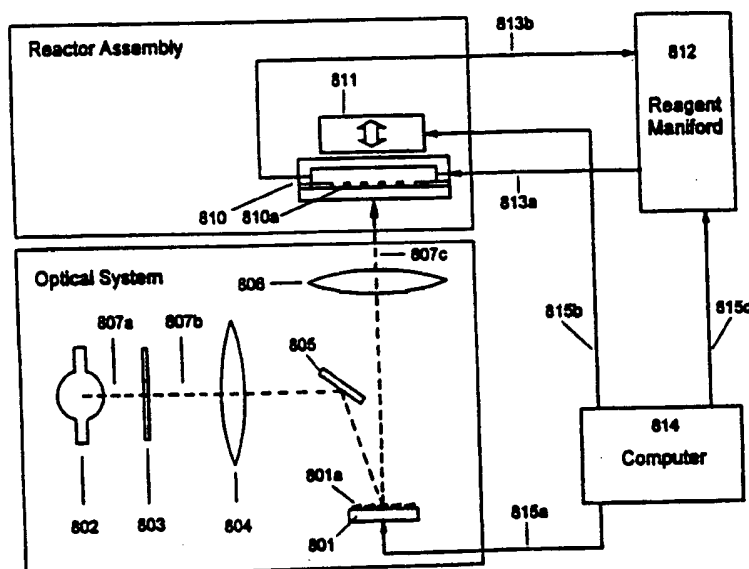




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(54) Title: METHOD AND APPARATUS FOR CHEMICAL AND BIOCHEMICAL REACTIONS USING PHOTO-GENERATED REAGENTS



(57) Abstract

A method and apparatus for performing chemical and biochemical reactions in solution using *in situ* generated photo-products as reagent or co-reagent. Specifically, the method and apparatus have applications in parallel synthesis of molecular sequence arrays on solid surfaces. There is provided an apparatus for performing light controlled reactions. One of the applications of the apparatus is to control reactions on a solid surface containing a plurality of isolated reaction sites, such as wells (the reactor). Light patterns for effecting the reactions are generated using a computer and a digital optical projector (the optical module). Patterned light is projected onto specific sites on the reactor, where light controlled reactions occur. A preferred application provides the *in situ* generation of chemical/biochemical reagents that are used in the subsequent chemical and biochemical reactions in certain selected sites among the many possible sites present. One aspect of the claimed invention is to change solution pH by photo-generation of acid or bases in a controlled fashion. Another preferred application is the parallel synthesis of biopolymers, such as oligonucleotides and peptides, wherein the method and apparatus are used for selective de protection or coupling reactions.

AMENDED CLAIMS

[received by the International Bureau on 24 November 1999 (24.11.99);
original claims 1-18 cancelled; new claims 19-35 added (6 pages)]

19. A method of using photogenerated reagents in solution phase for deprotecting initiating moieties, said initiating moieties are attached to a solid surface, the method comprising:
 - a) adding a photochemical solution to said solid surface, said photochemical solution comprising at least one liquid solvent and one photogenerated reagent precursor; and
 - b) irradiating said photochemical solution thereby producing at least one reactive chemical reagent and whereby deprotecting said initiating moieties.
20. The method of claim 19 wherein said photochemical solution further containing additives for modifying chemical properties of said photochemical solution.
21. The method of claim 20 wherein said additives are selected from the group consisting of sensitizers and stabilizers.

22. A pre-irradiation method of using photogenerated reagents in solution phase for deprotecting initiating moieties, said initiating moieties are attached to a solid surface, the method comprising:
- a) irradiating a photochemical solution in a first zone, said photochemical solution comprising at least one liquid solvent and one photogenerated reagent precursor, thereby producing at least one reactive chemical reagent; and
 - b) transporting said reactive chemical reagent onto said solid surface in a second zone whereby deprotecting said initiating moieties.
23. The method of claim 22 wherein said reactive chemical reagent is transported by mass transfer means.
24. The method of claim 23 wherein said mass transfer means is selected from the group consisting of diffusion and fluid flow.
25. A method of using photogenerated reagents in solution phase for simultaneous deprotecting initiating moieties at a plurality of discrete reaction sites on a substrate, said discrete reaction sites containing one or more protected initiating moieties, the method comprising:
- a) adding a photochemical solution to said substrate, said photochemical solution comprising at least one liquid solvent and one photogenerated reagent precursor;
 - b) isolating said discrete reaction sites; and
 - c) irradiating a predetermined group of isolated discrete reaction sites whereby generating reactive reagents and deprotecting said initiating moieties at the irradiated isolated discrete reaction sites.
26. The method of claim 25 wherein said discrete reaction sites are isolated by isolation means.
27. The method of claim 26 wherein said isolation means is selected from the group consisting of sealable microwells and patterned nonwetting films.

28. The method of claim 25 wherein said predetermined group of isolated reaction sites is irradiated using a programmable light radiation means.
29. The method of claim 28 wherein said programmable light radiation means is a programmable light projection device comprising a programmable spatial optical modulator.
30. The method of claim 29 wherein said programmable spatial optical modulator is selected from the group consisting of digital micromirror device, reflective liquid crystal display device, and transmissive liquid crystal display device.
31. The method of claim 25 wherein said predetermined group of isolated reaction sites is irradiated in such a way that a predetermined irradiation dosage is applied to each said isolated reaction site using a programmable light radiation means thereby generating a predetermined amount of the reactive reagents at each said irradiated isolated reaction site.
32. A method of using photogenerated reagents in solution phase for performing simultaneous synthesis of an array of multimers of selected sequences at discrete reaction sites on a substrate, said discrete reaction sites containing one or more protected initiating moieties, the method comprising:
 - a) adding a photochemical solution to said substrate, said photochemical solution comprising at least one liquid solvent and one photogenerated reagent precursor;
 - b) isolating said discrete reaction sites;
 - c) irradiating a first predetermined group of the isolated discrete reaction sites thereby generating reactive reagents and deprotecting the initiating moieties at the irradiated isolated discrete reaction sites;
 - d) adding a first monomer to said substrate such that the deprotected initiating moieties form chemical bond with the monomer;

- e) adding a photochemical solution to said substrate, said photochemical solution comprising at least one liquid solvent and one photogenerated reagent precursor;
 - f) isolating the discrete reaction sites;
 - g) irradiating a second predetermined group of isolated discrete reaction sites thereby generating reactive reagents and deprotecting the initiating moieties at the irradiated isolated discrete reaction sites;
 - h) adding a second monomer to said substrate such that the deprotected initiating moieties form chemical bond with the monomer;
 - i) repeating steps e) – h) until said array of multimers of selected sequences is synthesized.
33. The method of claim 32 wherein said multimers are selected from the group consisting of oligonucleotides, peptides, and carbohydrates.
34. A method of using photogenerated reagents in solution phase for performing simultaneous synthesis of an array of oligonucleotides of selected sequences at discrete reaction sites on a substrate, said discrete reaction sites containing one or more acid-labile group protected initiating moieties, the method comprising:
- a) adding a photochemical solution to said substrate, said photochemical solution comprising at least one liquid solvent and one photogenerated acid precursor;
 - b) isolating said discrete reaction sites;
 - c) irradiating a first predetermined group of the isolated reaction sites thereby generating acid reagents and deprotecting the initiating moieties at the irradiated isolated discrete reaction sites;
 - d) adding a first monomer to said substrate such that the deprotected initiating moieties form chemical bond with the monomer;

- e) adding photochemical solution to said substrate, said photochemical solution comprising at least one liquid solvent and one photogenerated acid precursor;
 - f) isolating the discrete reaction sites;
 - g) irradiating a second predetermined group of isolated discrete reaction sites thereby generating acid reagents and deprotecting the initiating moieties at the irradiated isolated reaction sites;
 - h) adding a second monomer to the substrate such that the deprotected initiating moieties form chemical bond with the monomer;
 - i) repeating steps e) – h) until said array of oligonucleotides of selected sequences is synthesized.
35. A method of using photogenerated-activator reagents in solution phase for performing simultaneous synthesis of an array of oligonucleotides of selected sequences at discrete reaction sites on a substrate, said discrete reaction sites containing one or more protected initiating moieties, the method comprising:
- a) adding a deprotection solution to said substrate thereby deprotecting the initiating moieties;
 - b) adding a coupling solution to said substrate, said coupling solution comprising at least a liquid solvent, a first monomer, and a photogenerated-activator precursor;
 - c) isolating the discrete reaction sites;
 - d) irradiating a first predetermined group of the isolated discrete reaction sites thereby generating at least one activator reagent and coupling the first monomer to the deprotected initiating moieties;
 - e) adding a deprotection solution to said substrate thereby deprotecting the initiating moieties;

- f) adding a second coupling solution to said substrate, said second coupling solution comprising at least a liquid solvent, a second monomer, and a photogenerated-activator precursor;
- g) isolating the discrete reaction sites;
- h) irradiating a second predetermined group of the isolated reaction sites thereby generating at least one activator reagent and coupling the second monomer to the deprotected initiating moieties;
- i) repeating steps e) – h) until said array of oligonucleotides of predetermined sequences is synthesized.

STATEMENT UNDER ARTICLE 19

The Applicant herewith encloses Article 19 amendments. Original claims 1 to 18 have been canceled and amended claims 19 to 35 have been added. The claims have been amended to clarify the present invention. The amended claims reflect a single common general inventive concept as defined by the Examiner in Group II. All the new claims relate to methods of multimers synthesis on a substrate.